J. Burke
200791

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=> fil reg

COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.15       0.15

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=> e "d-lysine"/cn 5

E1            1     D-LYSINAMIDE,
O-(1,1-DIMETHYLETHYL)-N-(1-OXO-3-((TRIPHENYLME

THYL)THIO)PROPYL)-D-SERYL-O-(1,1-DIMETHYLETHYL)-D-THREONYL-D

-PHENYLALANYL-O-(1,1-DIMETHYLETHYL)-D-THREONYL-N6-((1,1-DIME
                    THYLETHOXY)CARBONYL)/CN
E2            1     D-LYSINAMIDE,
O-(1,1-DIMETHYLETHYL)-N-(3-MERCAPTO-1-OXOPROPY

L)-D-SERYL-O-(1,1-DIMETHYLETHYL)-D-THREONYL-D-PHENYLALANYL-O

-(1,1-DIMETHYLETHYL)-D-THREONYL-N6-((1,1-DIMETHYLETHOXY)CARB
                    ONYL)-D-LYSYL-D-TRYP/CN
E3            1 --> D-LYSINE/CN
E4            1     D-LYSINE D-TARTRATE (1:1)/CN
E5            1     D-LYSINE D-TARTRATE (2:1)/CN

=> s e3

L1            1 D-LYSINE/CN

=> e "poly-d-lysine"/cn 5

E1            1     POLY-D-HISTIDINE/CN
E2            1     POLY-D-HISTIDINE SRU/CN
E3            0 --> POLY-D-LYSINE/CN
E4            1     POLY-D-LYSINE HYDROBROMIDE/CN
E5            1     POLY-D-MANNURONATE/CN

=> e "poly-l-lysine"/cn 5

E1            1     POLY-L-LACTIDE SRU/CN
E2            1     POLY-L-LEUCINE/CN
E3            2 --> POLY-L-LYSINE/CN
E4            1     POLY-L-LYSINE HYDROBROMIDE-POLY(METHACRYLIC ACID)
COMPOUND/C
```

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                    N
E5          1       POLY-L-LYSINE HYDROGEN BROMIDE/CN

=> s e3

L2          2 POLY-L-LYSINE/CN

=> fil medl,caplus,biosis,embase,wpids

COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                          ENTRY     SESSION
FULL ESTIMATED COST                                        7.40        7.55

FILE 'MEDLINE' ENTERED AT 13:46:41 ON 30 NOV 1999

FILE 'CAPLUS' ENTERED AT 13:46:41 ON 30 NOV 1999
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FILE 'WPIDS' ENTERED AT 13:46:41 ON 30 NOV 1999
COPYRIGHT (C) 1999 DERWENT INFORMATION LTD

=> s kidney(w)(reten? or accret? or accumulat?) and (l1 or l2 or d lysine or
poly d lysine)

L3          0 FILE MEDLINE
L4          1 FILE CAPLUS
L5          0 FILE BIOSIS
L6          0 FILE EMBASE
L7          0 FILE WPIDS

TOTAL FOR ALL FILES
L8          1 KIDNEY(W)(RETEN? OR ACCRET? OR ACCUMULAT?) AND (L1 OR L2 OR D
              LYSINE OR POLY D LYSINE)

=> d cbib abs


L8   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 1999 ACS
1992:443633   Document No. 117:43633  Reduced hepatic accumulation of
     radiolabeled monoclonal antibodies with
indium-111-thioether-poly-L-lysine-
     DTPA-monoclonal antibody-TP41.2F(ab')2.  Wang, Theodore S. T.; Fawwaz,
     Rashid A.; Aldersón, Philip O. (Columbia-Presbyt. Med. Cent., Columbia
     Univ., New York, NY, 10032, USA).  J. Nucl. Med., 33(4), 570-4 (English)
     1992.  CODEN: JNMEAQ.  ISSN: 0161-5505.
AB   In an attempt to improve bifunctional chelate labeling of Mab, the use of
     a polyamino acid backbone was studied for multiple DTPA substitutions.
     Poly(L-lysine) (PL) (3.8 Kd, n = 25) was partially acetylated with MADTPA
     to yield 11 mol of DTPA per mol of PL.  The av. nos. of DTPA on PL were
     directly quantified with MADTPA-C-14.  The remaining .epsilon.-amino
     groups on PL-DTPA (I) were measured with TNBS reagent.  A selective
     maleimide derivatization of I with S-SMPB yielded (II), which contains
2.3
```

mol of meleimido groups per mol of I. The sulfhydryl activation of Mab-TP41.2F(ab')2 with 2-Iminothiolane hydrochloride produced III, contg. 1.3 mol of sulfhydryl groups per mol of Mab. II and III) were combined to form a single thioether-spaced chain linkage of Mab-PL-DTPA, which was subsequently chelated with 111In to yield IV, which was the compd. of interest. Indium-111-PL-DTPA and 111In-DTPA-MabTP41.2F(ab')2 (V) also were prepd. for control studies. Direct cell binding assay revealed the mean immunoreactivity of IV to be 79.4% and that of V to be 39.5%. In a biodistribution study on melanoma tumor-bearing athymic mice at 4, 24, and 48 h postinjection, the tumor/blood and tumor/liver ratios at 48 h were 11.6 and 1.2 for (V), compared to 3.7 and 0.13, resp., with V. Thus, the PL configuration for radiolabeled antibodies seems to result in decreased hepatic accumulation and retained tumor avidity. The findings suggest that further studies of this new compd. are warranted.

=> s kidney and ((peptide or protein or polypeptide or glycoprotein or lipopotein or antibod?)(w)conjugat?) and (imag? or cytotoxic agent or ribonuclease or or onconase)

MISSING TERM 'OR OR'
The search profile that was entered contains a logical operator followed immediately by another operator.

=> s kidney and ((peptide or protein or polypeptide or glycoprotein or lipopotein or antibod?)(w)conjugat?) and (imag? or cytotoxic agent or ribonuclease or onconase)

L9	10	FILE MEDLINE
L10	61	FILE CAPLUS
L11	4	FILE BIOSIS
L12	11	FILE EMBASE
L13	3	FILE WPIDS

TOTAL FOR ALL FILES
L14 89 KIDNEY AND ((PEPTIDE OR PROTEIN OR POLYPEPTIDE OR GLYCOPROTEIN OR LIPOPOTEIN OR ANTIBOD?)(W) CONJUGAT?) AND (IMAG? OR CYTOTOXIC AGENT OR RIBONUCLEASE OR ONCONASE)

=> logoff hold

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	55.48	63.03

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.54	-0.54

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	ENTRY	SESSION
FULL ESTIMATED COST	55.48	63.03

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.54	-0.54

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=> di shis

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"HELP COMMANDS" at an arrow prompt (=>).

=> dis his


     (FILE 'HOME' ENTERED AT 13:45:15 ON 30 NOV 1999)

     FILE 'REGISTRY' ENTERED AT 13:45:54 ON 30 NOV 1999
                E "D-LYSINE"/CN 5
L1            1 S E3
                E "POLY-D-LYSINE"/CN 5
                E "POLY-L-LYSINE"/CN 5
L2            2 S E3

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, WPIDS' ENTERED AT 13:46:41 ON 30
     NOV 1999
L3            0 FILE MEDLINE
L4            1 FILE CAPLUS
L5            0 FILE BIOSIS
L6            0 FILE EMBASE
L7            0 FILE WPIDS
     TOTAL FOR ALL FILES
L8            1 S KIDNEY(W)(RETEN? OR ACCRET? OR ACCUMULAT?) AND (L1 OR L2 OR
D
L9           10 FILE MEDLINE
L10          61 FILE CAPLUS
L11           4 FILE BIOSIS
L12          11 FILE EMBASE
L13           3 FILE WPIDS
     TOTAL FOR ALL FILES
L14          89 S KIDNEY AND ((PEPTIDE OR PROTEIN OR POLYPEPTIDE OR
GLYCOPROTEI

=> s l14 and (l1 or l2 or poly(w)(l or d)(w)lysine)

L15           0 FILE MEDLINE
L16           3 FILE CAPLUS
L17           0 FILE BIOSIS
L18           0 FILE EMBASE
L19           0 FILE WPIDS

TOTAL FOR ALL FILES
L20           3 L14 AND (L1 OR L2 OR POLY(W)(L OR D)(W) LYSINE)

=> d 1-3 cbib abs;s behr t?/au,in;s goldenberg d?/au,in


L20  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 1999 ACS
1996:681542   Document No. 125:317395  Lysine and polylysine for reduced renal
     uptake of antibody fragments.  Behr, Thomas M.; Goldenberg, David M.
     (Center for Molecular Medicine and Immunology, USA).  PCT Int. Appl. WO
     9629087 A1 19960926, 37 pp  DESIGNATED STATES: W:  AL, AM, AT, AU, AZ,
BB,
     BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE,
     KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,
     PL, PT, RO, RU, SD, SE, SG, SI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM,
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DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US3308 19960320. PRIORITY: US 1995-407899 19950321.

AB **Kidney** uptake of antibody fragment conjugates in patients undergoing radioimmunodiagnosis, immunotherapy, or radioimmunotherapy is reduced by administration of the patient of one or more compds. selected from the group consisting of lysine and/or polylysine, pharmaceutically acceptable salts or carboxyl derivs. thereof. Human patients undergoing radioimmunodetection with 99mTc-labeled Fab' fragments of two anti-carcinoembryonic antigen antibodies were infused over a 3-h period with a com. amino acid soln. contg. 1.75 g L-lysine. A decrease of **kidney** uptake of radiolabeled fragments was obsd., the effect being more pronounced at 24 h than at 4 h post injection. However, **poly(L-lysine)** with a mol. wt. of 1-4 kDa reduced **kidney** uptake with a single i.p. injection at lower doses than the monomer. The potency of **poly(L-lysine)** increased with increasing mol. wt.

L20 ANSWER 2 OF 3 CAPLUS COPYRIGHT 1999 ACS

1989:420196 Document No. 111:20196 Modification of monoclonal antimyosin antibody: enhanced specificity of localization and scintigraphic visualization in acute experimental myocardial infarction. Khaw, Ban An; Torchilin, Vladimir P.; Klibanov, A. L.; Nossiff, Naseem D.; Powers, James B.; Strauss, H. William; Haber, Edgar (Div. Nucl. Med., Massachusetts Gen. Hosp., Boston, MA, USA). J. Mol. Cell. Cardiol., 21(Suppl. 1), 31-5 (English) 1989. CODEN: JMCDAY. ISSN: 0022-2828.

AB Pos. charged polymers have been shown to interact nonselectively with cells in vitro by means of an electrostatic binding to a neg. charged cell surface. It was reasoned that, if a net neg. charge could be introduced onto an antibody mol., some of the nonspecific antibody interactions with cells could be avoided without affecting the function of the antibody combining site. An important result would be improved target-to-background ratios should such antibodies be used as in vivo **imaging** agents. To test this hypothesis, bifunctional chelators, such as DTPA, were reacted with cationic polylysine polymers to permit radiolabeling with 111In, and then the polymer was rendered completely anionic by reacting the residual epsilon amino groups with succinic anhydride. These modified polymers were then covalently linked either to monoclonal antimyosin antibody or to its Fab fragment by means of a water-sol. carbodiimide. The immunoreactivity of the antibody-polymer conjugates was not significantly diminished. 111In-labeled antimyosin Fab modified with succinylated polylysine permitted visualization of exptl. myocardial infarcts as early as 30 min after i.v. injection. An inverse exponential relation was obsd. between the distribution of 201Tl and that of polymer-modified antimyosin Fab. 111In-labeled succinylated polymer administered by itself did not localize in the infarct. These observations suggest that anionically modified antibodies may enhance the specificity of antibody **imaging**.

L20 ANSWER 3 OF 3 CAPLUS COPYRIGHT 1999 ACS

1988:68965 Document No. 108:68965 Diagnostic and therapeutic **antibody conjugates** with active agents and aminodextran or polypeptide, methods for their preparation, and compositions containing them. Shih, Lisa B.; Primus, F. James; Goldenberg, M. David (Center for Molecular Medicine and Immunology, USA). PCT Int. Appl. WO 8705031 A1 19870827, 22 pp. DESIGNATED STATES: W: AU, DK, JP, NO, US; RW: AT, BE,

CH, DE, FR, GB, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1987-US406 19870225. PRIORITY: US 1986-833204 19860225.

AB A diagnostic or therapeutic agent (e.g. a drug, toxin, chelator, B compd., or label) is loaded onto a polymeric carrier (e.g. aminodextran or polypeptide) which in turn is site-specifically conjugated to a targeting antibody directed to a target tissue or organ where the diagnostic or therapeutic effect is realized. Dextran was partially oxidized with NaIO4, coupled to 1,3-diamino-2-hydroxypropane, and the product was reduced with NaBH4 and conjugated with N-hydroxysuccinimide-activated methotrexate and then with NaIO4-oxidized monoclonal antibody to carcinoembryonic antigen. The conjugate was administered i.v. for treatment of small-cell carcinoma with diffuse metastases in the lungs.

'IN' IS NOT A VALID FIELD CODE
L21 71 FILE MEDLINE
L22 73 FILE CAPLUS
L23 132 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L24 73 FILE EMBASE
L25 11 FILE WPIDS

TOTAL FOR ALL FILES
L26 360 BEHR T?/AU,IN

'IN' IS NOT A VALID FIELD CODE
L27 567 FILE MEDLINE
L28 285 FILE CAPLUS
L29 892 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L30 449 FILE EMBASE
L31 19 FILE WPIDS

TOTAL FOR ALL FILES
L32 2212 GOLDENBERG D?/AU,IN

=> s l26 and l32

L33 31 FILE MEDLINE
L34 32 FILE CAPLUS
L35 67 FILE BIOSIS
L36 34 FILE EMBASE
L37 1 FILE WPIDS

TOTAL FOR ALL FILES
L38 165 L26 AND L32

=> s l38 and (kidney or renal)

L39 12 FILE MEDLINE
L40 13 FILE CAPLUS
L41 14 FILE BIOSIS
L42 10 FILE EMBASE
L43 1 FILE WPIDS

TOTAL FOR ALL FILES
L44 50 L38 AND (KIDNEY OR RENAL)

=> s l44 not (l20 or l8)

L45 12 FILE MEDLINE
L46 12 FILE CAPLUS
L47 14 FILE BIOSIS
L48 10 FILE EMBASE
L49 1 FILE WPIDS

TOTAL FOR ALL FILES
L50 49 L44 NOT (L20 OR L8)

=> dup rem l50

PROCESSING COMPLETED FOR L50
L51 23 DUP REM L50 (26 DUPLICATES REMOVED)

=> d cbib abs 1-23

L51 ANSWER 1 OF 23 CAPLUS COPYRIGHT 1999 ACS
1999:740269 Low- versus high-dose radioimmunotherapy with humanized anti-CD22 or chimeric anti-CD20 antibodies in a broad spectrum of B cell-associated malignancies. **Behr, Thomas M.**; Wormann, Bernhard; Gramatzki, Martin; Riggert, Joachim; Gratz, Stefan; Behe, Martin; Griesinger, Frank; Sharkey, Robert M.; Kolb, Hans-J.; Hiddemann, Wolfgang; **Goldenberg, David M.**; Becker, Wolfgang (Departments of Nuclear Medicine, Georg-August-University of Gottingen, Gottingen, D-37075, Germany). Clin. Cancer Res., 5(10, Suppl.), 3304s-3314s (English) 1999. CODEN: CCREF4. ISSN: 1078-0432. Publisher: American Association for Cancer Research.
AB Both CD22 and CD20 have been used successfully as target mols. for radioimmunotherapy (RAIT) of low-grade B cell non-Hodgkin's lymphoma. Because both CD20 and CD22 are highly expressed relatively early in the course of B cell maturation, and because its expression is maintained up to relatively mature stages, we studied the potential of the humanized anti-CD22 antibody, hLL2, as well as of the chimeric anti-CD20 (chCD20) antibody, rituximab (IDEC-C2B8), for low- or high-dose (myeloablative) RAIT of a broad range of B cell-assocd. hematol. malignancies. A total of 10 patients with chemorefractory malignant neoplasms of B cell origin were studied with diagnostic (n = 5) and/or potentially therapeutic doses (n = 9) of hLL2 (n = 4; 0.5 mg/kg, 8-315 mCi of 131I) or chCD20 (n = 5; 2.5 mg/kg, 15-495 mCi of 131I). The diagnostic doses were given to establish the patients' eligibility for RAIT and to est. the individual radiation dosimetry. One patient suffered of Waldenstrom's macroglobulinemia, eight patients had low- (n = 4), intermediate- (n = 2) or high- (n = 2) grade non-Hodgkin's lymphoma, and one patient had a chemore-factory acute lymphatic leukemia, after having failed five heterologous bone marrow or stem cell transplantations. Three of these 10 patients were scheduled for treatment with conventional (30-63 mCi, cumulated doses of up to 90 mCi of 131I) and 7 with potentially myeloablative (225-495 mCi of 131I) activities of 131I-labeled hLL2 or chCD20 (0.5 and 2.5 mg/kg, resp.); homologous (n = 6) or heterologous (n = 1) stem cell support was provided in these cases. Good tumor targeting was obsd. in all diagnostic as well as posttherapeutic scans of all patients. In myeloablative therapies, the therapeutic activities were calcd. based on the diagnostic radiation

dosimetry, aiming at lung and **kidney** doses .ltoreq. 20Gy. Stem cells were reinfused when the whole-body activity retention fell below 20 mCi. In eight assessable patients, five had complete remissions, two experienced partial remissions (corresponding to an overall response rate of 87%), and one (low-dose) patient had progressive disease despite therapy. In the five assessable, actually stem-cell grafted patients, the complete response rate was 100%. Both CD20 and CD22 seem to be suitable target mols. for high-dose RAIT in a broad spectrum of hematol. malignancies of B cell origin with a broad range of maturation stages (from acute lymphatic leukemia to Waldenstrom's macroglobulinemia). The better therapeutic outcome of patients undergoing high-dose, myeloablative RAIT favors this treatment concept over conventional, low-dose regimens.

L51 ANSWER 2 OF 23 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.

1999367297 EMBASE Low- versus high-dose radioimmunotherapy with humanized anti-CD22 or chimeric anti-CD20 antibodies in a broad spectrum of B cell-associated malignancies. **Behr T.M.**; Wormann B.; Gramatzki M.; Riggert J.; Gratz S.; Behe M.; Griesinger F.; Sharkey R.M.; Kolb H.-J.; Hiddemann W.; **Goldenberg D.M.**; Becker W.. T.M. Behr, Department of Nuclear Medicine, Georg-August-University of Gottingen, Robert-Koch-Strasse 40, D-37075 Gottingen, Germany. tmbehr@med.uni-goettingen.de. Clinical Cancer Research 5/10 SUPPL. (3304s-3314s) 1999.

Refs: 24.

ISSN: 1078-0432. CODEN: CCREF4. Pub. Country: United States. Language: English. Summary Language: English.

AB Both CD22 and CD20 have been used successfully as target molecules for radioimmunotherapy (RAIT) of low-grade B cell non-Hodgkin's lymphoma. Because both CD20 and CD22 are highly expressed relatively early in the course of B cell maturation, and because its expression is maintained up to relatively mature stages, we studied the potential of the humanized anti-CD22 antibody, hLL2, as well as of the chimeric anti-CD20 (chCD20) antibody, rituximab (IDEC-C2B8), for low- or high-dose (myeloablative) RAIT of a broad range of B cell-associated hematological malignancies. A total of 10 patients with chemorefractory malignant neoplasms of B cell origin were studied with diagnostic (n = 5) and/or potentially therapeutic doses (n = 9) of hLL2 (n = 4; 0.5 mg/kg, 8-315 mCi of 131I) or chCD20 (n = 5; 2.5 mg/kg, 15-495 mCi of 131I). The diagnostic doses were given to establish the patients' eligibility for RAIT and to estimate the individual radiation dosimetry. One patient suffered of Waldenstrom's macroglobulinemia, eight patients had low(n = 4), intermediate- (n = 2) or high- (n = 2) grade non-Hodgkin's lymphoma, and one patient had a chemorefractory acute lymphatic leukemia, after having failed five heterologous bone marrow or stem cell transplantations. Three of these 10 patients were scheduled for treatment with conventional (30-63 mCi, cumulated doses of up to 90 mCi of 131I) and 7 with potentially myeloablative (225-495 mCi of 131I) activities of 131I-labeled hLL2 or chCD20 (0.5 and 2.5 mg/kg, respectively); homologous (n = 6) or heterologous (n = 1) stem cell support was provided in these cases. Good tumor targeting was observed in all diagnostic as well as posttherapeutic scans of all patients. In myeloablative therapies, the therapeutic activities were calculated based on the diagnostic radiation dosimetry, aiming at lung and **kidney** doses .ltoreq. 20Gy. Stem cells were reinfused when the whole-body activity retention fell below 20 mCi. In eight assessable patients, five had complete remissions, two experienced partial remissions (corresponding to an overall response rate of 87%), and

one (low-dose) patient had progressive disease despite therapy. In the five assessable, actually stem-cell grafted patients, the complete response rate was 100%. Both CD20 and CD22 seem to be suitable target molecules for high-dose RAIT in a broad spectrum of hematological malignancies of B cell origin with a broad range of maturation stages (from acute lymphatic leukemia to Waldenstrom's macroglobulinemia). The better therapeutic outcome of patients undergoing high-dose, myeloablative RAIT favors this treatment concept over conventional, low-dose regimens.

L51 ANSWER 3 OF 23 MEDLINE DUPLICATE 1
1999290654 Document Number: 99290654. High-linear energy transfer (LET) alpha versus low-LET beta emitters in radioimmunotherapy of solid tumors: therapeutic efficacy and dose-limiting toxicity of 213Bi- versus 90Y-labeled CO17-1A Fab' fragments in a human colonic cancer model.
Behr T M; Behe M; Stabin M G; Wehrmann E; Apostolidis C; Molinet R; Strutz F; Fayyazi A; Wieland E; Gratz S; Koch L; **Goldenberg D M**; Becker W. (Department of Nuclear Medicine, Georg-August-University, Gottingen, Germany.. tmbehr@med.uni-goettingen.de). CANCER RESEARCH, (1999 Jun 1) 59 (11) 2635-43. Journal code: CNF. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Recent studies suggest that radioimmunotherapy (RIT) with high-linear energy transfer (LET) radiation may have therapeutic advantages over conventional low-LET (e.g., beta-) emissions. Furthermore, fragments may be more effective in controlling tumor growth than complete IgG. However, to the best of our knowledge, no investigators have attempted a direct comparison of the therapeutic efficacy and toxicity of a systemic targeted therapeutic strategy, using high-LET alpha versus low-LET beta emitters in vivo. The aim of this study was, therefore, to assess the toxicity and antitumor efficacy of RIT with the alpha emitter 213Bi/213Po, as compared to the beta emitter 90Y, linked to a monovalent Fab' fragment in a human colonic cancer xenograft model in nude mice. Biodistribution studies of 213Bi- or 88Y-labeled benzyl-diethylene-triamine-pentaacetate-conjugated Fab' fragments of the murine monoclonal antibody CO17-1A were performed in nude mice bearing s.c. human colon cancer xenografts. 213Bi was readily obtained from an "in-house" 225Ac/213Bi generator. It decays by beta- and 440-keV gamma emission, with a t(1/2) of 45.6 min, as compared to the ultra-short-lived alpha emitter, 213Po (t(1/2) = 4.2 micros). For therapy, the mice were injected either with 213Bi- or 90Y-labeled CO17-1A Fab', whereas control groups were left untreated or were given a radiolabeled irrelevant control antibody. The maximum tolerated dose (MTD) of each agent was determined. The mice were treated with or without inhibition of the **renal** accretion of antibody fragments by D-lysine (T. M. Behr et al., Cancer Res., 55: 3825-3834, 1995), bone marrow transplantation, or combinations thereof. Myelotoxicity and potential second-organ toxicities, as well as tumor growth, were monitored at weekly intervals. Additionally, the therapeutic efficacy of both 213Bi- and 90Y-labeled CO17-1A Fab' was compared in a GW-39 model metastatic to the liver of nude mice. In accordance with **kidney** uptake values of as high as > or = 80% of the injected dose per gram, the **kidney** was the first dose-limiting organ using both 90Y- and 213Bi-labeled Fab' fragments. Application of D-lysine decreased the **renal** dose by >3-fold. Accordingly, myelotoxicity became dose limiting with both conjugates. By using lysine protection, the MTD of 90Y-Fab' was 250

microCi and the MTD of 213Bi-Fab' was 700 microCi, corresponding to blood doses of 5-8 Gy. Additional bone marrow transplantation allowed for an increase of the MTD of 90Y-Fab' to 400 microCi and for 213Bi-Fab' to 1100 microCi, respectively. At these very dose levels, no biochemical or histological evidence of **renal** damage was observed (**kidney** doses of <35 Gy).. At equitoxic dosing, 213Bi-labeled Fab' fragments were significantly more effective than the respective 90Y-labeled conjugates. In the metastatic model, all untreated controls died from rapidly progressing hepatic metastases at 6-8 weeks after tumor inoculation, whereas a histologically confirmed cure was observed in 95% of those animals treated with 700 microCi of 213Bi-Fab' 10 days after model induction, which is in contrast to an only 20% cure rate in mice treated with 250 microCi of 90Y-Fab'. These data show that RIT with alpha emitters may be therapeutically more effective than conventional beta emitters. Surprisingly, maximum tolerated blood doses were, at 5-8 Gy, very similar between high-LET alpha and low-LET beta emitters. Due to its short physical half-life, 213Bi appears to be especially suitable for use in conjunction with fast-clearing fragments.

L51 ANSWER 4 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
1999:318762 Document No.: PREV199900318762. Experimental studies on the therapeutic efficacy and toxicity of alpha- as compared to beta-emitters in radioimmunotherapy. **Behr, T. M. (1)**; Behe, M. (1); Stabin, M. G. (1); Wehrmann, E. (1); Apostolidis, C. (1); Molinet, R. (1); Koch, L. (1); **Goldenberg, D. M. (1)**; Becker, W. (1). (1) Georg-August-University of Goettingen, Goettingen Germany. Journal of Nuclear Medicine, (May, 1999) Vol. 40, No. 5 SUPPL., pp. 313P. Meeting Info.: 46th Annual Meeting of the Society of Nuclear Medicine Los Angeles, California, USA June 6-10, 1999 Society of Nuclear Medicine. ISSN: 0161-5505. Language: English.

L51 ANSWER 5 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
1999:71386 Document No.: PREV199900071386. Methods for reduced **renal** uptake of antibody fragments. **Behr, T. M.; Goldenberg, D. M.**. Bloomfield, N.J. USA. ASSIGNEE: CENTER FOR MOLECULAR MEDICINE AND IMMUNOLOGY. Patent Info.: US 5843894 Dec. 1, 1998. Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 1, 1998) Vol. 1217, No. 1, pp. 528. ISSN: 0098-1133. Language: English.

L51 ANSWER 6 OF 23 MEDLINE DUPLICATE 2
1998351600 Document Number: 98351600. Experimental studies on the role of antibody fragments in cancer radio-immunotherapy: Influence of radiation dose and dose rate on toxicity and anti-tumor efficacy. **Behr T M** ; Memtsoudis S; Sharkey R M; Blumenthal R D; Dunn R M; Gratz S; Wieland E; Nebendahl K; Schmidberger H; **Goldenberg D M**; Becker W. (Department of Nuclear Medicine, Georg-August-University, Gottingen, Germany.. tmbehr@WisLAN1.med.uni-goettingen.de). INTERNATIONAL JOURNAL OF CANCER, (1998 Aug 31) 77 (5) 787-95. Journal code: GQU. ISSN: 0020-7136. Pub. country: United States. Language: English.
AB Whereas bivalent fragments have been widely used for radio-immunotherapy, no systematic study has been published on the therapeutic performance of monovalent conjugates in vivo. The aim of our study was, therefore, to determine the therapeutic performance of (131)I-labeled Fab as compared to bivalent conjugates and to analyze factors that influence dose-limiting organ toxicity and anti-tumor efficacy. The maximum tolerated doses (MTDs) and dose-limiting organ toxicities of the (131)I-labeled anti-CEA antibody

MN-14 [IgG, F(ab')2 and Fab] were determined in nude mice bearing s.c. human colon cancer xenografts. Mice were treated with or without bone marrow transplantation (BMT) or inhibition of the **renal** accretion of antibody fragments by D-lysine or combinations thereof. Toxicity and tumor growth were monitored. Radiation dosimetry was calculated from biodistribution data. With all 3 (131)I-labeled immunoconjugates [IgG, F(ab')2 and Fab], the red marrow was the only dose-limiting organ; MTDs were 260 microCi for IgG, 1,200 microCi for F(ab')2 and 3 mCi for Fab, corresponding to blood doses of 17 Gy, 9 Gy and

4 Gy, respectively. However, initial dose rates were 10 times higher with Fab as compared to IgG and 3 times higher as compared to F(ab')2. The MTD of all 3 immunoconjugates was increased by BMT by approximately 30%. In accordance with **renal** doses below 10 Gy, no signs of nephrotoxicity were observed. Despite lower absorbed tumor doses, at equitoxic dosing, Fab fragments were more effective at controlling tumor growth than the respective bivalent fragment or IgG, probably due to higher intratumoral dose rates. Our data indicate that the improved anti-tumor effectiveness of antibody fragments as compared to IgG and the higher myelotoxicity at comparably lower red marrow doses are most likely due to the higher initial dose rates observed with antibody fragments.

L51 ANSWER 7 OF 23 MEDLINE DUPLICATE 3

1998139512 Document Number: 98139512. Reducing the **renal** uptake of radiolabeled antibody fragments and peptides for diagnosis and therapy: present status, future prospects and limitations. **Behr T M; Goldenberg D M;** Becker W. (Department of Nuclear Medicine, Georg-August-University of Gottingen, Robert-Koch-Strasse 40, D-37075 Gottingen, Germany.)EUROPEAN JOURNAL OF NUCLEAR MEDICINE, (1998 Feb) 25 (2) 201-12. Ref: 41. Journal code: ENC. ISSN: 0340-6997. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Elevated **renal** uptake and prolonged retention of radiolabeled antibody fragments and peptides is a problem in the therapeutic application of such agents. Over recent years, one of the focuses of research has therefore been to develop suitable methods to reduce this **renal** uptake, and to evaluate whether the resulting methodology will benefit therapy with antibody fragments and peptides. In these studies it has been shown that the **kidney** uptake of antibody fragments in animals can be reduced in a dose-dependent manner by almost one order of magnitude by the systemic administration of cationic amino acids and their derivatives, whereas the uptake in all other organs, as well as the tumor, remains unaffected. A similar reduction in **renal** retention is achieved for all intracellularly retained radionuclides (e.g., radiometals) or radioiodinated immunoconjugates, as well as for smaller peptides. Lysine is usually the preferred agent, and its d- and l-isomers are equally effective whether given intraperitoneally

or orally. Amino sugars are effective, but their N-acetyl derivatives, lacking the positive charge, are not. Basic polypeptides are also effective, and their potency increases with increasing molecular weight (i.e., the amount of positive charges per molecule). Urine analysis of treated individuals shows the excretion of unmetabolized, intact fragments

or peptides, in contrast to mostly low-molecular-weight metabolites in untreated controls. In therapy studies using radiometal-conjugated Fab fragments, the **kidney** is the first dose-limiting organ. Administration of cationic amino acids results in a substantial increase in the maximum tolerated dose of such Fab fragments. No biochemical or histological evidence of **renal** damage has been observed under these conditions. As was the case in animal studies, in pilot clinical trials the **renal** uptake in patients injected with Fab' fragments

and given amino acids could be decreased significantly, whereas the uptake by all other organs remained unaffected. These recent studies indicate that a variety of basic compounds are capable of inhibiting the tubular reabsorption of peptides and proteins, thus significantly lowering the **renal** uptake of antibody fragments or peptides in both animals and patients. On a molecular basis, the effect seems to rely essentially on the presence of a positively charged amino group. Thus, radiation nephrotoxicity of antibody fragments and peptides can be overcome successfully; this may provide new prospects for cancer therapy with radiolabeled antibody fragments and peptides.

L51 ANSWER 8 OF 23 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 4
1998:440577 Document No. 129:213535 Reducing **renal** accretion of radiolabeled antibody fragments and peptides: improvement of therapeutic efficacy by overcoming nephrotoxic potential? A review. **Behr, Thomas M.; Goldenberg, David M.**; Becker, Wolfgang (Department of Nuclear Medicine, Georg-August University, Gottingen, D-37075, Germany). Tumor Targeting, 3(1), 2-12 (English) 1998. CODEN: TUTAF9. ISSN: 1351-8488. Publisher: Stockton Press.

AB A review with 29 refs. Elevated **renal** uptake and extended retention of radiolabeled antibody fragments and peptides is a problem in the therapeutic application of such agents. In recent years a focus of our research was to develop methods to reduce **renal** accretion, to evaluate whether the resulting methodol. would benefit therapy with antibody fragments, and to compare the anti-tumor efficacy of antibody fragments to the whole IgG. The **kidney** uptake of Fab1 fragments in animals could be reduced by cationic amino acids and their derivs. in a dose-dependent manner by almost one order of magnitude as compared with untreated controls. The uptake in all other organs, as well as the tumor, remained unaffected. A similar redn. in **renal** retention was seen for all other intracellularly retained isotopes or radioiodinated conjugates, as well as in F(ab)2 fragments. D and L isomers of lysine were equally effective whether given i.p. (i.p.) or orally. D-glucosamine was effective, but its N-acetyl deriv., lacking the pos. charge, was not. Basic polypeptides were also effective; their potency increased with increasing mol. wt. High performance liq. chromatog. (HPLC) of the urine taken from lysine-treated animals showed the excretion of intact Fab, in contrast to mostly low mol. wt. metabolites in the control group. In therapy studies using 90Y-Fab fragments, the **kidney** was the first dose-limiting organ. Application of lysine enabled an increase in the max. tolerated dose by 25%, because myelotoxicity became dose limiting. By using bone marrow transplantation and lysine, the max. tolerated dose was doubled, where no biochem. or histol. evidence of **renal** damage was obsd. The max. tolerated dose of F(ab)2 fragments could be elevated only by the combination of bone marrow transplantation and lysine. With IgG the bone marrow alone was dose limiting. Fab was more therapeutically effective than F(ab)2, consistent with its more favorable dosimetry, and was also more effective than IgG, probably due to a higher dose rate and potentially due to a more homogeneous distribution. In a pilot clin. trial, the **renal** uptake of patients injected with 99mTc-Fab1 and given amino acids was significantly lower than in the control group, whereas the uptake of all other organs remained unaffected. These studies indicate that a variety of basic compds. are capable of inhibiting the tubular reabsorption of peptides and proteins, thus significantly lowering the **kidney** uptake of antibody fragments or peptides in animals as well as patients. On a mol. basis, the effect seems to rely essentially on the presence of a

pos. charged amino group. Therefore radiation nephrotoxicity can be overcome successfully, thereby substantially increasing the anti-tumor efficacy. Further studies with radiometal-conjugated antibody fragments and peptides are necessary to det. the MTD, the dose-limiting organs, anti-tumor effectiveness, as well as the nephroprotective effects of cationic amino acids in humans.

L51 ANSWER 9 OF 23 MEDLINE DUPLICATE 5

1998068549 Document Number: 98068549. Overcoming the nephrotoxicity of radiometal-labeled immunoconjugates: improved cancer therapy administered to a nude mouse model in relation to the internal radiation dosimetry. **Behr T M**; Sharkey R M; Sgouros G; Blumenthal R D; Dunn R M; Kolbert K; Griffiths G L; Siegel J A; Becker W S; **Goldenberg D M**. (Garden State Cancer Center at the Center for Molecular Medicine and Immunology, Belleville, New Jersey, USA.)CANCER, (1997 Dec 15) 80 (12 Suppl) 2591-610. Journal code: CLZ. ISSN: 0008-543X. Pub. country: United States. Language: English.

AB BACKGROUND: Elevated **renal** uptake and extended retention of radiolabeled antibody fragments and peptides is a problem in the therapeutic application of such agents. However, cationic amino acids have been shown to reduce **renal** accretion. The aims of the current study were to evaluate whether this methodology would benefit therapy with yttrium 90 (90Y)-labeled antibody fragments (Fab, F(ab)2), to establish the relationship between radiation dosimetry and observed biologic effects, and to compare the antitumor efficacy of antibody fragments with that of whole immunoglobulin (Ig)G. METHODS: The maximum tolerated dose (MTD) and the dose-limiting organ toxicity of 90Y-labeled anti-carcinoembryonic antigen (CEA) MN-14 monoclonal antibodies (Fab, F(ab)2, and IgG) were determined in nude mice bearing GW-39 human colon carcinoma xenografts. The mice were treated with or without **kidney** protection by administration of D-lysine, with or without bone marrow transplantation (BMT), or with combinations of each. Toxicity and tumor growth were monitored at weekly intervals after radioimmunotherapy. Dosimetry was calculated from biodistribution studies using 88Y-labeled antibody. Three different dosimetric models were examined: 1) taking solely self-to-self doses into account, using S factors for 90Y in spheroids from 0.1 to 1 g; 2) correcting for cross-organ radiation; and 3) using actual mouse anatomy as represented by nuclear magnetic resonance imaging with a three-dimensional internal dosimetry package (3D-ID). RESULTS: The **kidney** was the first dose-limiting organ with the use of Fab fragments. Acute radiation nephritis occurred at injected activities > or = 325 microCi, and chronic nephrosis at doses > or = 250 microCi. Activities of 200 microCi were tolerated by 100% of the animals (i.e., the MTD). Application of lysine decreased the **renal** dose by approximately fivefold, facilitating a 25% increase in the MTD (to 250 microCi), because myelotoxicity became dose-limiting despite red marrow doses of less than 5 gray (Gy). By using BMT and lysine, the MTD could be doubled from 200 to 400 microCi, where no biochemical or histologic evidence of **renal** damage was observed (**kidney** dose, < or = 40 Gy). With injected activities of > or = 325 microCi without **kidney** protection, and with a hepatic self-to-self dose of only 4 Gy, rising liver enzymes were observed, which could be explained only by cross-organ radiation from radioactivity in the **kidneys** (in the immediate neighborhood of the right **kidney** up to > or = 150 Gy). The MTD of F(ab)2 fragments could be elevated only by a combination of BMT and lysine. With IgG, the bone marrow alone was dose-limiting. Tumor

dosimetry correlated well with antitumor effects; Fab was more effective than F(ab)2, which was consistent with its more favorable dosimetry, and it may also be more effective than IgG due to its higher dose rate and more homogenous distribution. Dosimetry Model 1 was insufficient for predicting biologic effects. Model 2 seemed to be more accurate, accounting for interorgan crossfire. However, Model 3 showed an additional substantial contribution to the red bone marrow dose due to crossfire from the abdominal organs. CONCLUSIONS: These data show that radiation nephrotoxicity is an important effect of cancer therapy with radiometal-conjugated antibody fragments or peptides. However, this effect can be overcome successfully with the application of cationic amino acids, which substantially increase the anti-tumor efficacy of radiometal-labeled immunoconjugates. For understanding the biologic effects (e.g., liver toxicity) of 90Y in a mouse model, accounting for cross-organ radiation is essential. Further studies with radiometal-conjugated monoclonal antibody fragments and peptides are necessary to determine the MTD, dose-limiting organs, antitumor effectiveness, and nephroprotective effects of cationic amino acids in humans.

L51 ANSWER 10 OF 23 MEDLINE DUPLICATE 6

97403091 Document Number: 97403091. Development of a streptavidin-anti-carcinoembryonic antigen antibody, radiolabeled biotin pretargeting method for radioimmunotherapy of colorectal cancer. Studies in a human colon cancer xenograft model. Sharkey R M; Karacay H; Griffiths G L; **Behr T M**; Blumenthal R D; Mattes M J; Hansen H J; **Goldenberg D M.** (Garden State Cancer Center, Belleville, New Jersey 07109, USA.)BIOCONJUGATE CHEMISTRY, (1997 Jul-Aug) 8 (4) 595-604. Journal code: A1T. ISSN: 1043-1802. Pub. country: United States. Language: English.

AB Pretargeting methodologies can produce high tumor:blood ratios, but their role in cancer radioimmunotherapy (RAIT) is uncertain. A pretargeting method was developed using a streptavidin (StAv) conjugate of MN-14 IgG, an anti-carcinoembryonic antigen (CEA) murine monoclonal antibody (mab) as the primary targeting agent, an anti-idiotype antibody (WI2 IgG) as a clearing agent, and DTPA- or DOTA-conjugated biotin as the radiolabeled targeting agent. A variety of reagents and conditions were examined to optimize this method. At 3 h, 111In-DTPA-peptide-biotin tumor uptake was 3.9 +/- 0.8% per gram and tumor:blood ratios were > 11:1. By 24 h, this ratio was 178:1, but tumor accretion declined in accordance with the gradual loss of StAv-MN-14 from the tumor. Tissue retention was highest in the liver and **kidneys**, but their tumor:organ ratios were > 2:1. Dosimetry predicted that radiolabeled MN-14 alone would deliver higher tumor doses than this pretargeting method. Increasing the specific activity and using DOTA-biotin in place of DTPA increased tumor uptake nearly 2-fold, but analysis of StAv-MN-14's biotin-binding capacity indicated over 90% of the initial biotin-binding sites were blocked within 24 h. Animals fed a biotin-deficient diet had 2-fold higher 111In-DOTA-biotin uptake in the tumor, but higher uptake also was observed in all normal tissues. Although exceptionally adept at achieving high tumor:blood ratios rapidly, the tumor uptake of radiolabeled biotin with

this pretargeting method is significantly ($p < 0.0001$) lower than that with a radiolabeled antibody. Endogenous biotin and enhanced liver and **kidney** uptake may limit the application of this method to RAIT, especially when evaluating the method in animals, but with strategies to overcome these limitations, this pretargeting method could be an effective therapeutic alternative.

L51 ANSWER 11 OF 23 MEDLINE
97388458 Document Number: 97388458. Selection of radioimmunoconjugates for the therapy of well-established or micrometastatic colon carcinoma. Sharkey R M; Blumenthal R D; **Behr T M**; Wong G Y; Haywood L; Forman D; Griffiths G L; **Goldenberg D M**. (Garden State Cancer Center, Belleville, NJ 07109, USA.)INTERNATIONAL JOURNAL OF CANCER, (1997 Jul 29) 72 (3) 477-85. Journal code: GQU. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB In order to optimize radioimmunotherapy (RAIT) as a cancer-treatment modality, it is necessary to select the appropriate radionuclide and antibody carrier. We evaluated the therapeutic potential of a single cycle of Mu-9 anti-CSAp monoclonal antibody (MAb) labeled with 3 different radionuclides, 131I, 90Y and 188Re. Intact antibodies and bivalent fragments with different blood clearance kinetics, normal organ distribution and varying tumor accretion and retention are also evaluated.

Efficacy of treatment for large and small tumor burden was assessed in nude mice bearing s.c. GW-39 human colonic-carcinoma xenografts or intrapulmonary micrometastatic GW-39 colonies at the maximal tolerated dose of each agent. The magnitude and duration of myelosuppression associated with each radioantibody was considered by monitoring peripheral blood counts, marrow colony-forming unit activity and hematopoietic tissue weight. Radiation-dose estimates were calculated based on the kinetics of antibody accretion and elimination from tumor and normal tissues, and the results were correlated with tumoricidal activity and dose-limiting toxicity results. These studies, therefore, represent a detailed analysis, in a well-defined experimental tumor system, of several parameters (antibody form, radioisotope, tumor size) influencing the overall outcome of RAIT using equitoxic doses. It was found that myelosuppression is the primary dose-limiting toxicity for all radioantibodies except 90Y-F(ab')2, even though the different agents showed varied organ distribution. In a single-cycle treatment schedule of Mu-9 MAb, the 131I-labeled IgG is the radioimmunoconjugate of choice for the treatment of s.c. and intrapulmonary growth of the GW-39 human colonic-carcinoma xenograft in nude mice.

L51 ANSWER 12 OF 23 MEDLINE DUPLICATE 7
97239474 Document Number: 97239474. Radioimmunotherapy of solid tumors: a review "of mice and men". **Behr T M; Goldenberg D M;** Becker W S. (Department of Nuclear Medicine, Georg-August-University of Gottingen, Germany.)HYBRIDOMA, (1997 Feb) 16 (1) 101-7. Ref: 27. Journal code: GFS. ISSN: 0272-457X. Pub. country: United States. Language: English.

AB Radioimmunotherapy in lymphoma is crossing the threshold to become a standard mode of treatment. Whereas in solid tumors in preclinical studies, radioimmunotherapy has proven to be superior to conventional

chemotherapy, clinical success is still limited. The purpose of this brief review is to analyze recent developments in preclinical as well as clinical radioimmunotherapy of solid, CEA-expressing tumors. Advances in experimental radioimmunotherapy are characterized by the development of metastatic, rather than subcutaneous, tumor models in nude mice, which seem to reflect the actual clinical situation much more accurately. Furthermore, the recent development of strategies to reduce the **renal** accretion of antibody fragments and peptides enables the use of such smaller molecules for therapy, especially those also labeled with radiometals and other forms of intracellularly retained radionuclides. Recent developments in clinical radioimmunotherapy are characterized by a trend toward the treatment of small-volume and micrometastatic disease, as is the case, e.g., in adjuvant settings. Interestingly, despite dramatic differences in size, weight and percent-of-injected-dose-per-gram uptake values, only small differences between animal models and the actual patient situation exist with respect to activity concentrations (in microCi/gram) in the tumors and tissues. Because the activity concentration over time determines the radiation absorbed dose, and thus biological effects, we postulate that animal models should be able to predict actual clinical scenarios fairly well. These findings could be used as guidelines in the design of future preclinical, as well as clinical, trials.

L51 ANSWER 13 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
1997:326028 Document No.: PREV199799625231. Complete versus fragmented, 131I- and 90Y-labeled antibodies for radioimmunotherapy (RAIT) of CEA-expressing cancers: Influence of dose rate and **renal** accretion on toxicity and anti-tumor-efficacy. **Behr, T. M. (1)**; Memtsoudis, S. (1); Blumenthal, R. D.; Dunn, R. M.; Sharkey, R. M.; **Goldenberg, D. M.** ; Becker, W. (1). (1) Dep. Nuclear Med., Univ. Goettingen, Goettingen Germany. Journal of Nuclear Medicine, (1997) Vol. 38, No. 5 SUPPL., pp. 31P. Meeting Info.: 44th Annual Meeting of the Society of Nuclear Medicine San Antonio, Texas, USA June 1-5, 1997 ISSN: 0161-5505. Language: English.

L51 ANSWER 14 OF 23 MEDLINE
96221193 Document Number: 96221193. Improved prospects for cancer therapy with radiolabeled antibody fragments and peptides? [editorial; comment] [see comments]. **Behr T M; Goldenberg D M.** JOURNAL OF NUCLEAR MEDICINE, (1996 May) 37 (5) 834-6. Journal code: JEC. ISSN: 0161-5505. Pub. country: United States. Language: English.

L51 ANSWER 15 OF 23 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 1996-454840 [45] WPIDS
AB WO 9629087 A UPAB: 19961111
Use of 1 cpd. (I) selected from D-lysine, poly-D-lysine, poly-L-lysine and their salts and carboxyl derivs. is claimed for reducing **kidney** uptake of antibody (Ab) fragment conjugates or radiolabelled Ab fragments, in a radioimmunodiagnosis or immunotherapy involving injection of an Ab fragment conjugate or radiolabelled Ab fragment. Also claimed is the use of (I) for prepn. of an agent for use as above.

(I) is administered parenterally (specifically by continuous infusion or by 1 bolus injection) in aq. soln., or orally. The poly-D- or -L-lysine

has mol. wt. 15-30 kDa. The AB fragment conjugate is radiolabelled (esp. with an imaging isotope for use in radioimmunodiagnosis) or contains a cytotoxic agent for use in immunotherapy.

ADVANTAGE - Admin. of (I) markedly reduces **renal** uptake and retention of radioisotopes (which can reduce diagnostic accuracy, as well as causing radiation nephritis) and cytotoxic agents (which can cause **kidney** damage). (I) are less toxic, and require fewer and lower doses than prior art agents. Typically (I) reduce **renal** uptake and retention of radioisotopes by a factor of 3, allow clear detection and imaging of a tumour or infectious lesion otherwise obscured by high background radiation around the **kidney** (esp. when using short imaging times of 1-5 hrs.) and allow use of a 2-3 fold higher dose of conjugate than could otherwise be used without risk of **kidney** damage.

Dwg.0/7

L51 ANSWER 16 OF 23 MEDLINE DUPLICATE 8

96221192 Document Number: 96221192. Reduction of **renal** uptake of monoclonal antibody fragments by amino acid infusion [see comments]. **Behr T M**; Becker W S; Sharkey R M; Juweid M E; Dunn R M; Bair H J; Wolf F G; **Goldenberg D M**. (Garden State Cancer Center, Center for Molecular Medicine and Immunology, Newark, New Jersey 07103-2763, USA.

)JOURNAL OF NUCLEAR MEDICINE, (1996 May) 37 (5) 829-33. Journal code: JEC. ISSN: 0161-5505. Pub. country: United States. Language: English.

AB The **renal** uptake of radiolabeled antibody fragments and peptides presents a problem in radioimmunodetection and therapy, compromising lesion sensitivity, especially with intracellularly-retained isotopes. Previously, we showed that cationic amino acids and their derivatives are capable of significantly reducing **kidney** uptake in animals. We report our initial clinical results of successful **renal** uptake reduction in five patients who underwent cancer radioimmunodetection with 99mTc-anti-CEA Fab' fragments. METHODS: The patients were infused with two liters of a commercially-available nutritive amino acid solution (containing approximately 2.25 g/liter lysine-glutamate and 2.50 g/liter arginine), whereas 75 control patients received the same volume of saline (quantification of organ and tumor kinetics from conjugate whole-body views by ROI technique). RESULTS: The **renal** uptake in the amino acid group was significantly lower ($p<0.05$) than in the control group (11.1 +/- 2.0% injected dose versus 17.7 +/- 7.0% injected dose at 24 hr postinjection), whereas the uptake of all other organs remained unaffected. Gel filtration chromatography of the urine taken from amino-acid-treated patients showed that a significantly higher amount of excreted activity was bound to intact Fab' (53% of excreted activity) in contrast to only less than 10% in the control group. CONCLUSION: The **renal** uptake of monoclonal antibody fragments in patients can be reduced significantly by amino acid infusion, even at considerably lower doses than those that were safe and effective in animals. As was found in animals, the mechanism seems to rely on an inhibition of the re-absorption of tubularly-filtered proteins by the proximal tubule cells. These results encourage further clinical trials to lower the **renal** uptake experienced in radioimmunodetection, as well as in therapeutic trials with antibody fragments and peptides.

L51 ANSWER 17 OF 23 MEDLINE DUPLICATE 9

96266937 Document Number: 96266937. Clinical evaluation of tumor targeting with the anticarcinoembryonic antigen murine monoclonal antibody fragment,

MN-14 F(ab)2. Juweid M; Sharkey R M; **Behr T M**; Swayne L C; Dunn R; Ying Z; Siegel J A; Hansen H J; **Goldenberg D M**. (Garden State Cancer Center at the Center for Molecular Medicine and Immunology, Newark, New Jersey 07103, USA.)CANCER, (1996 Jul 1) 78 (1) 157-68. Journal code: CLZ. ISSN: 0008-543X. Pub. country: United States. Language: English.

AB BACKGROUND: The initial clinical experience with the second-generation, high-affinity, MN-14 immunoglobulin (IgG) anticarcinoembryonic antigen (CEA) monoclonal antibody (MoAb) in patients with CEA-producing tumors was reported previously. A bivalent fragment of this MoAb, MN-14 F(ab)2, was prepared, and its pharmacokinetics, targeting properties, dosimetry, and immunogenicity were investigated. METHODS: MN-14 F(ab)2(0.6-29 mg) was labeled with 131I(7.7-269 millicuries and injected into 28 patients with CEA-producing cancers. External scintigraphy was used to evaluate tumor targeting. Quantitative external scintigraphy methods were used to determine the organ and tumor radiation doses. RESULTS: The overall sensitivity of tumor targeting on a lesion basis was 86%, similar to that reported previously for MN-14 whole IgG. The biologic T1/2's for the fragment in the blood and total body (in hours) were 16.8 +/- 4.1 and 59.4 +/- 9.4, respectively, compared with 27.3 +/- 15.7 and 69.6 +/- 32.2 reported for MN-14 IgG. Depending on the protein dose given, high plasma CEA levels (>100ng/ML) resulted in a significant alteration of MoAb pharmacokinetics and organ dosimetry. Individual tumors received an average dose of 10.7 +/- 7.3 centigray [cGy]/mCi, and the tumor-to-total body, red marrow, lung, liver, and **kidney** dose ratios were 16.8 +/- 11.1, 5.6 +/- 3.6, 5.1 +/- 3.9, 6.0 +/- 3.8, and 3.1 +/- 2.0, respectively (mean + standard deviation [SD]). Only 9 of 18 patients (50%) injected with >4 mg (range: 4-52.1 mg) of MN-14 F(ab)2 developed significant levels of human antimouse antibodies, suggesting that the F(ab)2 may be less immunogenic than the intact IgG. CONCLUSIONS: MN-14 F(ab)2 exhibits a similar targeting sensitivity and tumor dose as reported previously for the IgG form. The lower red marrow doses combined with lower immunogenicity expected for this agent, may make it a suitable alternative for future imaging and therapeutic applications.

L51 ANSWER 18 OF 23 MEDLINE DUPLICATE 10

96075400 Document Number: 96075400. Targeting of liver metastases of colorectal cancer with IgG, F(ab')2, and Fab' anti-carcinoembryonic antigen antibodies labeled with 99mTc: the role of metabolism and kinetics. **Behr T**; Becker W; Hannappel E; **Goldenberg D M**; Wolf F. (Department of Nuclear Medicine, Friedrich-Alexander-University of Erlangen-Nuremberg, Germany.)CANCER RESEARCH, (1995 Dec 1) 55 (23 Suppl) 5777s-5785s. Journal code: CNF. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The aim of this study was to investigate targeting of the liver metastases by directly 99mTc-labeled complete (IgG) and fragmented antibodies [F(ab')2 and Fab'] in relation to their kinetics and metabolic fate. A total of 127 patients with metastatic colorectal cancer were examined [IgG1, BW 431/26 (Behringwerke, Marburg, Germany) n = 50; F(ab')2, F023C5 (Sorin Biomedica, Saluggia, Italy) n = 58; Fab', IMMU-4 (Immunomedics, Morris Plains, NJ) n = 19]. Native monoclonal antibodies (MAbs), serum samples from 10 min to 24 h postinjection (p.i.), and urine were analyzed by gel filtration chromatography. Kinetic data were deduced from whole-body and single-photon emission computed tomographic scans, performed 10 min to 24 h p.i. (region-of-interest technique). In BW

431/26, 96% of injected activity was labeled IgG1; in F023C5, 29% was F(ab')2, and 71% was Fab'; and in IMMU-4, 92% was Fab', and 8% was F(ab')2. Serum half-lives were: IgG1, 36 h (liver uptake predominant); F(ab')2, 16 h; and Fab', 4 h (**renal** uptake predominant). All MAbs were metabolized, fragments more rapidly than IgG, to low-molecular-weight products and excreted into the urine (e.g., Tc-cystine). In targeting liver metastases, sensitivities were found to be higher for fragments (44.1, 72.5, and 80% for BW 431/26, F023C5, and IMMU-4, respectively) but at significantly lower tumor:background ratios than with IgG (1.78 +/- 0.29 versus 1.29 +/- 0.11 and 1.43 +/- 0.53; P < 0.01). With IgG, there was a continuous tumor uptake over 24 h, whereas with fragments, the maximal uptake occurred mostly within 1 h, with subsequent clearance being slower for antigen-bound activity than for nonspecific background. Hence, diagnosis was possible mostly after 4 h with fragments but often not before 24 h with IgG. These results show that the higher sensitivity of fragments in liver lesion targeting at earlier p.i. times does not rely on an increased antibody uptake but on a more rapid clearance of nonspecific background activity due to faster metabolism and excretion. Intact MAbs show a slow, continuous uptake, leading to higher tumor:background ratios at later p.i. times, often beyond the imaging possibilities of 99mTc.

L51 ANSWER 19 OF 23 CAPLUS COPYRIGHT 1999 ACS

1995:969271 Document No. 124:80930 Targeting of liver metastases of colorectal cancer with IgG, F(ab')2, and Fab' anti-carcinoembryonic antigen antibodies labeled with 99mTc: the role of metabolism and kinetics. **Behr, Thomas**; Becker, Wolfgang; Hannappel, Ewald; **Goldenberg, David M.**; Wolf, Friedrich (Departments of Nuclear Medicine and Biochemistry, Friedrich-Alexander-University of Erlangen-Neuremberg, Erlangen, D-91054, Germany). Cancer Res., 55(23, Suppl.), 5777S-85S (English) 1995. CODEN: CNREA8. ISSN: 0008-5472.

AB The aim of this study was to investigate targeting of the liver metastases by directly 99mTc-labeled complete (IgG) and fragmented antibodies [F(ab')2 and Fab'] in relation to their kinetics and metabolic fate. A total of 127 patients with metastatic colorectal cancer were examd. [IgG1, BW 431/26 (Behringwerke, Marburg, Germany) n = 50; F(ab')2, F023C5 (Sorin Biomedica, Saluggia, Italy) n = 58; Fab', IMMU-4 (Immunomedics, Morris Plains, NJ) n = 19]. Native monoclonal antibodies (MAbs), serum samples from 10 min to 24 h postinjection (p.i.), and urine were analyzed by gel filtration chromatog. Kinetic data were deduced from whole-body and single-photon emission computed tomog. scans, performed 10 min to 24 h p.i. (region-of-interest technique). In BW 431/26, 96% of injected activity was labeled IgG1; in F023C5, 29% was F(ab')2, and 71% was Fab'; and in IMMU-4, 92% was Fab', and 8% was F(ab')2. Serum half-lives were: IgG1, 36 h (liver uptake predominant); F(ab')2, 16 h; and Fab', 4 h (**renal** uptake predominant). All MAbs were metabolized, fragments more rapidly than IgG, to low-mol.-wt. products and excreted into the urine (e.g., Tc-cystine). In targeting liver metastases, sensitivities were found to be higher for fragments (44.1, 72.5, and 80% for BW 431/26, F023C5, and IMMU-4, resp.) but at significantly lower tumor:background ratios than with IgG (1.78 .+-. 0.29 vs. 1.29 .+-. 0.11 and 1.43 .+-. 0.53; P < 0.01). With IgG, there was a continuous tumor uptake over 24 h, whereas with fragments, the maximal uptake occurred mostly within 1 h, with subsequent clearance being slower for antigen-bound activity than for nonspecific background. Hence, diagnosis was possible mostly after 4 h

with fragments but often not before 24 h with IgG. These results show that the higher sensitivity of fragments in liver lesion targeting at earlier p.i. times does not rely on an increased antibody uptake but on a more rapid clearance of nonspecific background activity due to faster metab. and excretion. Intact MAbs show a slow, continuous uptake, leading to higher tumor:background ratios at later p.i. times, often beyond the imaging possibilities of 99mTc.

L51 ANSWER 20 OF 23 MEDLINE DUPLICATE 11

95368640 Document Number: 95368640. Reduction of the **renal** uptake of radiolabeled monoclonal antibody fragments by cationic amino acids and their derivatives. **Behr T M**; Sharkey R M; Juweid M E; Blumenthal R D; Dunn R M; Griffiths G L; Bair H J; Wolf F G; Becker W S; **Goldenberg D M.** (Garden State Cancer Center, Center for Molecular Medicine and Immunology, Newark, New Jersey 07103-2763, USA.)CANCER RESEARCH, (1995 Sep 1) 55 (17) 3825-34. Journal code: CNF. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The **renal** uptake of radiolabeled antibody fragments and peptides is a problem in radioimmunodetection and radioimmunotherapy, especially with intracellular retained radiometals. The aim of this study was to develop suitable methods to reduce this **kidney** uptake. BALB/c mice or nude mice bearing the human GW-39 colon carcinoma xenograft were given i.p. injections of basic amino acids or a range of different basic amino acid derivatives, amino sugars, as well as cationic peptides. The effect of these agents on the biodistribution of Fab' and F(ab')2 fragments of different mAbs radiolabeled with 99mTc, 188Re, 111In, 88Y, or 125I was studied. Tumor and organ uptake was determined and compared to untreated mice. The **kidney** uptake of Fab' fragments was reduced 5-6-fold in a dose-dependent manner as compared to untreated controls. The uptake in all other organs, as well as the tumor, was unaffected. A similar reduction in **renal** retention was seen for all other intracellularly retained isotopes, as well as for F(ab')2 fragments. D- and L-isomers of lysine were equally effective whether given i.p. or p.o. D-glucosamine was effective, but its N-acetyl derivative was not. Basic polypeptides (e.g., poly-L-lysine) were also effective; their potency increased with increasing molecular weight. HPLC of the urine taken from treated animals showed the excretion of intact Fab', in contrast to mostly low-molecular-weight metabolites in the control group. These studies indicate that a variety of basic compounds is capable of inhibiting the tubular reabsorption of peptides and proteins, thus lowering the **kidney** uptake of antibody fragments significantly. On a molecular basis, the effect seems to essentially rely on the presence of a positively charged amino group. By reducing **renal** retention of antibody fragments, their role as imaging and therapeutic agents may be expanded.

L51 ANSWER 21 OF 23 CAPLUS COPYRIGHT 1999 ACS

1995:783642 Document No. 123:221932 Reduction of the **renal** uptake of radiolabeled monoclonal antibody fragments by cationic amino acids and their derivatives. **Behr, Thomas M.**; Sharkey, Robert M.; Juweid, Malik E.; Blumenthal, Rosalyn D.; Dunn, Robert M.; Griffiths, Gary L.; Bair, Hans-J.; Wolf, Friedrich G.; Becker, Wolfgang S.; **Goldenberg, David M.** (Garden State Cancer Cent. Cent. Mol. Med. Immunol., Newark, NJ, 07103-2763, USA). Cancer Res., 55(17), 3824-34 (English) 1995. CODEN: CNREA8. ISSN: 0008-5472.

AB The **renal** uptake of radiolabeled antibody fragments and peptides is a problem in radioimmunodetection and radioimmunotherapy, esp. with

intracellularly retained radiometals. The aim of this study was to develop suitable methods to reduce this **kidney** uptake. BALB/c mice or nude mice bearing the human GW-39 colon carcinoma xenograft were given i.p. injections of basic amino acids or a range of different basic amino acid derivs., amino sugars, as well as cationic peptides. The effect of these agents on the biodistribution of Fab' and F(ab')2 fragments of different mAbs radiolabeled with 99mTc, 188Re, 111In, 88Y, or 125I was studied. Tumor and organ uptake was detd. and compared to untreated mice. The **kidney** uptake of Fab' fragments was reduced 5-6-fold in a dose-dependent manner as compared to untreated controls. The uptake in all other organs, as well as tumor, was unaffected. A similar redn. in **renal** retention was seen for all other intracellularly retained isotopes, as well as for F(ab')2 fragments. D- And L-isomers of lysine were equally effective whether given i.p. or p.o. D-Glucosamine was effective, but its N-acetyl derivs. was not. Basic polypeptides (e.g., poly-L-lysine) were also effective; their potency increased with increasing mol. wt. HPLC of the urine taken from treated animals showed the excretion of intact Fab', in contrast to mostly low-mol.-wt. metabolites in the control group. These studies indicate that a variety of basic compds. is capable of inhibiting the tubular resorption of peptides and proteins, thus lowering the **kidney** uptake of antibody fragments significantly. On a mol. basis, the effect seems to essentially rely on the presence of a pos. charged amino group. By reducing **renal** retention of antibody fragments, their role as imaging and therapeutic agents may be expanded.

L51 ANSWER 22 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
1995:187844 Document No.: PREV199598202144. Reduction of **kidney** uptake of Fab' fragments of monoclonal antibodies: Animal experiments and initial clinical results. **Behr, T. M.**; Sharkey, R. M.; Juweid, M. E.; Aninipot, R.; **Goldenberg, D. M.**. Garden State Cancer Cent., Newark, NJ 07103 USA. Proceedings of the American Association for Cancer Research Annual Meeting, (1995) Vol. 36, No. 0, pp. 617. Meeting Info.: Eighty-sixth Annual Meeting of the American Association for Cancer Research Toronto, Ontario, Canada March 18-22, 1995 ISSN: 0197-016X. Language: English.

L51 ANSWER 23 OF 23 BIOSIS COPYRIGHT 1999 BIOSIS
1995:334321 Document No.: PREV199598348621. Reduction of **kidney** uptake of radiolabeled monoclonal antibody (MAb) fragments: Preclinical and initial clinical results. **Behr, T. M. (1)**; Sharkey, R. M. (1); Juweid, M.; Aninipot, R. (1); Griffiths, G. L.; **Goldenberg, D. M. (1)**. (1) Garden State Cancer Center, Newark, NJ USA. Journal of Nuclear Medicine, (1995) Vol. 36, No. 5 SUPPL., pp. 19P-20P. Meeting Info.: 42nd Annual Meeting of the Society of Nuclear Medicine Minneapolis, Minnesota, USA June 12-15, 1995 ISSN: 0161-5505. Language: English.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	102.79	110.34

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION